STAR-Liège Clinical Trial Interim Results:

Safe and Effective Glycemic Control for All

Vincent Uyttendaele*, Jennifer L. Knopp, Marc Pirotte, Philippe Morimont, Bernard Lambermont,

Geoffrey M. Shaw, Thomas Desaive, and J. Geoffrey Chase.

***Abstract*— While the benefits of glycemic control for critically ill patients are increasingly demonstrated, the ability to deliver safe, effective control to intermediate target ranges is widely debated due to the increased risk of hypoglycemia. This study analyzes interim clinical trial results of the fully computerized model-based Stochastic TARgeted (STAR) glycemic control framework at the University Hospital of Liège, Belgium. Patients with dysglycemia were randomly assigned to the full version of STAR, modulating both insulin and nutrition inputs, or STAR-IO, an insulin only version of STAR. Both arms target the normoglycemic 80-145 mg/dL (4.4-8.0 mmol/L) band. Results are further compared to retrospective data from 20 patients under the standard unit protocol targeting a higher 100-150 mg/dL (5.6-8.3 mmol/L) band. Much higher time in target band is provided under the full version of STAR, with similar safety and significantly lower incidence of mild hyperglycemia (blood glucose > 145 mg/dL or 8.0 mmol/L) and severe hyperglycemia (blood glucose > 180 mg/dL or 10.0 mmol/L). As a result, lower median blood glucose levels are safely and consistently achieved with lower glycemic variability, suggesting STAR's potential to improve clinical outcomes. These interim results show the possibility to achieve safe, effective control for all patients using STAR, and suggest glycemic control to lower targets could be beneficial.**

I. Introduction

Critically ill patients often experience hyperglycemia as a result of stress and inflammatory metabolic response to injury [1], which is associated with increased intensive care unit (ICU) morbidity and mortality [2]. Glycemic control (GC) using insulin therapy has improved patient outcomes, and reduced patient length of stay and clinical workload [3-6]. However, GC has been proven hard to achieve safely, leading to increased blood glucose (BG) variability and risk of hypoglycemia [7-9], also independently associated with increased morbidity and mortality [9-11]. As a result, the appropriate target band for glycemic

Research supported by the FRIA – Fund for Research Training in Industry and Agriculture, the EUFP7 and RSNZ Marie Curie IRSES program, the MedTech CoRE and TEC, and the NZ National Science Challenge 7. *Asterisk indicates corresponding author*.

*V. Uyttendaele is with the GIGA In-silico Medicine, University of Liège, Belgium and Department of Mechanical Engineering, University of Canterbury, New Zealand (e-mail: vincent.uyttendaele@uliege.be; vincent.uyttendaele@pg.canterbury.ac.nz).

J. L. Knopp, and J. G. Chase are with the Department of Mechanical Engineering, University of Canterbury, New Zealand.

G. M. Shaw is with the Department of Intensive Care, Christchurch Hospital, New Zealand.

T. Desaive is with the GIGA In-silico Medicine, University of Liège, Belgium.

M. Pirotte, P. Morimont, and B. Lambermont are with the University Hospital of Liège, Belgium.

control has been widely debated [12, 13], with the fear of hypoglycemia from GC being potentially more harmful than beneficial for the patients [14].

However, recent studies show model-based computerized GC methods successfully control BG to lower target bands without significantly increasing hypoglycemic risks [15, 16]. Such models use key physiological parameters and account for inter- and intra- patient variability [17-19]. Patient-specificity for GC solutions in ICUs have been shown essential for control quality and control [20]. Over the years, some critical factors have been identified for good protocol design, including safety, performance, compliance to protocol, and repeatability across units [16, 17, 21, 22]. More specifically, using a GC protocol design not providing these critical aspects can bias results [23].

The Stochastic TARgeted (STAR) GC framework uses physiological and stochastic models to uniquely dose both insulin and nutrition inputs [24, 25]. It identifies the patient-specific insulin sensitivity (SI) [26] and forecasts metabolic variability, offering a unique risk-based dosing approach accounting for inter- and intra- patient variability [24]. STAR is fully computerized, adjustable to different ICU practices, and has shown positive, near identical results in multiple centers, which no other protocol has done [16].

This paper analyzes interim clinical trial results of STAR in a Belgian ICU.

II. Methods

A. STAR-Liège Clinical Trial Design and Protocol

The STAR-Liège clinical trial is designed to evaluate the STAR framework for GC at the University Hospital of Liège, Belgium. Previous studies on STAR have shown safe and effective control achieved for nearly all patients, while providing better nutrition than most ICUs in the world [16, 27]. This trial includes two arms. The first uses an insulin-only version of STAR (STAR-IO), while the second modulates both enteral nutrition and insulin inputs using STAR. In STAR-IO, nutrition is left at clinician discretion, while in STAR, the nutrition rate is derived from a daily base rate of 2000 kcal/day nutritional intake, and adapted for GC [27].

Starting criteria is 2 consecutive BG measurements > 150 mg/dL (8.0 mmol/L). BG assays are via either blood gas analyzer or standard glucometers. Insulin is administered continuously through intravenous catheter, with increments of maximum 2 U/h, and limited to a maximum infusion rate of 9U/h. Enteral nutrition can be adjusted treatment to treatment by maximum 30% of the original 100% goal feed (GF) rate, going no lower than 30% of the original GF. The target band is 80-145 mg/dL (4.4-8.0 mmol/L). STAR is stopped either if the patient BG is stabilized for 6 hours (BG in target band and insulin $\leq$ 2 U/h) or after 72h

of treatment. The protocol is implemented on Android tablets at the patient bedside. The University Hospital of Liège Ethics Committee approved this trial (#**B707201733994**) and the use of collected data.

STAR uses patient clinical data to identify the patient-specific current SI level [26], using a clinically validated physiological model [28]. Potential future metabolic variability is then assessed based on this current SI level, using the stochastic model [25]. This probabilistic approach enables a forecast of the 5^{th}-95^{th} percentile range of likely future evolution of SI for the next 3 hours. Hence, a corresponding prediction of the 5^{th}-95^{th} percentile range for future BG evolution can be calculated for a given treatment. STAR thus determines the best insulin and nutritional interventions based on prediction of likely future BG that best overlaps the clinically chosen target band. Nutrition is reduced only if using insulin alone results in excessive predicted BG levels, giving a patient-specific indication of patient ability to tolerate glucose. STAR offers 1-3 hourly treatment options [16].

B. Protocol comparison analysis

To date, 6 patients were included in the full STAR arm and 11 in STAR-IO. The study compares GC results with retrospective data from 20 patients under the standard protocol. The standard protocol is table-based, targeting a higher 100-150 mg/dL (5.6-8.3 mmol/L) band, and BG measurements are typically taken 4-hourly [29]. Thus, it is expected to have slightly higher BG and lower workload. Statistics use hourly resampled BG.

Safety is assessed by the %BG < 80 mg/dL (4.4 mmol/L), %BG < 72 mg/dL (4.0 mmol/L, or mild hypoglycemia), %BG < 40 mg/dL (2.2 mmol/L, severe hypoglycemia), %BG

TABLE I. CLINICAL RESULTS SUMMARY FOR SAFETY, PERFORMANCE, AND COMPLIANCE TO PROTOCOL COMPARISON.

	STAR	***STAR-IO***	***Retro***
# Patients	6	11	20
Total hours	308	645	5006
Workload (meas/day)	12	16	7
Median BG (mg/dL)	117 [108 126]	121 [106 139]	139 [117 160]
Median ΔBG (mg/dL)	5 [2, 9]	7 [4, 14]	/
Median insulin (U/h)	3.5 [2.5 4.5]	3.5 [1.5 6.0]	2.5 [2.0 3.0]
Median dextrose (g/h)	7.1 [5.0 8.2]	8.1 [4.9 9.2]	9.8 [8.6 11.5]
% BG in 80-117 mg/dL	49.4	41.3	/
% BG in 80-145 mg/dL	90.1	77.9	55.4
% BG in 145-180 mg/dL	8.7	10.9	31.3

	STAR	***STAR-IO***	***Retro***
% BG > 180 mg/dL	0.3	9.8	12.0
% BG < 80 mg/dL	1.0	1.4	1.3
% BG < 72 mg/dL	1.0	0.5	0.5
% BG < 40 mg/dL	0	0	0
# Patients < 40 mg/dL	0	0	0
% intervention changed	1.4	10.2	21.3
% max option chosen	89.0	89.9	/
Median max. option avail.	3 [1 3]	1 [1 2]	/

Data given as median [IQR] as appropriate, divide by 18 for mmol/L.

in 145-180 mg/dL (8.0-10.0 mmol/L, or mild hyperglycemia), and %BG > 180 mg/dL (10.0 mmol/L, severe hyperglycemia). The number of patients experiencing severe hypoglycemia is also reported. Performance is evaluated by the median [interquartile range (IQR)] BG levels, and %BG in target band and the 80-117 mg/dL (4.4-6.5 mmol/L) intermediate range. Finally, protocol compliance is assessed by the number of interventions changed from the original recommendation.

III. Results

Clinical results are presented in Table 1 and Figure 1. Per-patient BG traces over time are in Figure 2.

STAR has lower, less variable, and tighter BG levels than STAR-IO (117 [108, 126] vs 121 [106, 139] mg/dL). The %BG in target band is significantly higher (90.1 vs 77.9%), and 8% more in the tighter 80-117 mg/dL range. High, similar safety is achieved for both STAR and STAR-IO, with less than 1.4% of BG below target band and no severe hypoglycemia. While %BG in mild hyperglycemia is similar (~10%), the %BG in severe hyperglycemia is significantly higher for STAR-IO (0.3% vs 9.8%).

Compliance to protocol is higher for STAR, with only 1.4% of interventions changed compared to 10.2% with STAR-IO. Nurses picked the maximum measurement interval option 90% of the time for both arms. These numbers are also reflected in the lower workload demand for STAR (12 vs 16 measurements per day). Median insulin infusion rates were similar for both arms (3.5 [2.5, 4.5] vs 3.5 [1.5, 6.0] U/h), but less variable for STAR. Finally, nutrition intake is slightly higher for STAR-IO (feed set by local standards and left at clinician discretion) compared to STAR (7.1 [5.0, 8.2] vs 8.1 [4.9, 9.2] g/h).

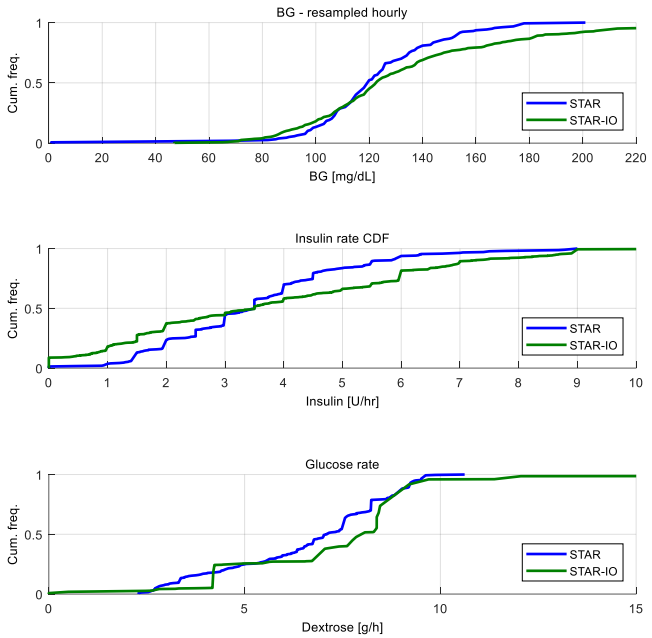

Figure 1. Cohort resampled BG, inuslin rate, and glucose rate cumulative distribution functions. Overall, BG achieved is lower and less variable (top) for STAR (blue) compared to STAR-IO (green), with lower insulin (middle) and nutrition (bottom) rates.

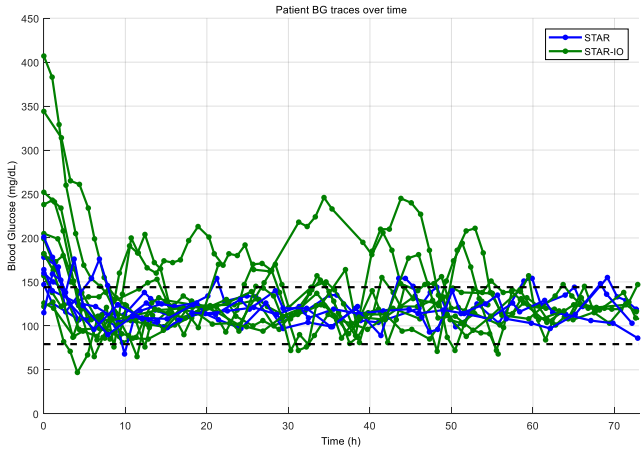

Figure 2. Patients BG traces evolution over time. Green lines show patients under the STAR-IO protocol and blue lines show patients under the full STAR protocol. Black dashed lines represent the target band.

The retrospective cohort median BG was higher (139 [117, 160] mg/dL), likely explained by the higher target band with lower insulin rates administered than STAR (2.5 [2.0, 3.0] U/h). Safety is comparable to STAR in terms of hypoglycemia, but there is much higher %BG in mild and severe hyperglycemic ranges (31.1% and 12.0% respectively). This result could also be explained by the higher nutrition rates (9.8 [8.6, 11.5] g/h). Workload is much lower (7 measurements per day), but protocol compliance is lower, with up to 21.3% of interventions changed.

Overall, the full version of STAR achieved safer, more effective control with high nutrition intake and lower workload than STAR-IO. The high compliance to protocol suggests the STAR framework to be adopted.

IV. Discussion

While STAR-IO shows high safety and performance compared to the standard protocol, the full version of STAR clearly achieves better glycemic control outcomes through modulation of nutrition in addition to insulin. Typically, STAR better controls more resistant patients by slightly lowering carbohydrate intake to safely bring BG into the safe target band, where STAR-IO will fail to control their persistent hyperglycemia in the same case. This key difference has a direct impact on both the increased time in target band and lower workload. This unique risk-based dosing approach, controlling both inputs, also reduces glycemic variability. Most importantly, despite controlling nutrition, STAR has been shown to provide better caloric intake than most ICU in the world [27].

Starting BG are higher in patients receiving GC under STAR-IO, as shown in Figure 2. This may contribute to the higher %BG > 180 mg/dL. However, Figure 2 shows STAR is also much more effective at maintaining BG in the target range once it is inside. This improved performance is likely due to feed modulation, where persistent hyperglycemia is treated with feed reductions in addition to insulin. A case study is shown in Figure 3, where glucose-insulin interventions and outcomes are shown for a patient on STAR and another on STAR-IO. In Patient A, on STAR, feed is first increased to 100% GF then reduced to ~30% after 6 hours of GC. Underlying SI allows STAR to reduce nutrition rates where it will not be tolerated, as would be indicated by persistent hyperglycemia. Hence, this temporary lower dextrose rate is safer for the patient. By hour 31, nutrition rate is progressively increased back to 100% GF as the patient metabolism is better able to handle higher dextrose intake. In contrast, Patient B nutrition rate is kept constant (as per clinical guidelines), resulting in consistent high BG levels, above, or close to the upper target band limit, with higher associated insulin rates. This may often lead to hypoglycemia and higher glycemic variability if patient SI changes due to underlying condition, or other clinical interactions.

The small number of patients included to date may impact the results. Only 6 patients were in the full STAR protocol and 11 in STAR-IO. However, these patients come from the same ICU population, and are reflective of the general population with similar median [IQR] identified SI levels for both groups ($3.4x10^{-4}$ [$2.7x10^{-4}$, $4.2x10^{-4}$] for STAR vs $3.5x10^{-4}$ [$2.5x10^{-4}$, $5.8x10^{-4}$] L/mU/min for STAR-IO).

The difference in protocol compliance could be explained by two main factors. First, the first patients were included in the STAR-IO protocol. The STAR framework was new to clinical staff, and potentially induced a fear of change and, thus, the greater (10%) interventions changed handled control. Second, the lower target band used by STAR may have affected clinical

staff fear of hypoglycemia. In contrast, the 1.4% interventions changed in the full STAR arm were only modifications due to conflict with ICU guidelines limiting the maximum increase in nutrition rate.

Although the retrospective protocol target band is clearly higher than STAR (100-150 mg/dL), risks of hypoglycemia are similar. However, the %BG above 145 mg/dL and the severe hyperglycemic threshold of 180 mg/dL are also much higher. Additionally, the %BG in band for this protocol is only 54% compared to 77-90% for STAR. This is achieved with much lower workload (7 vs 12 measurements per day),

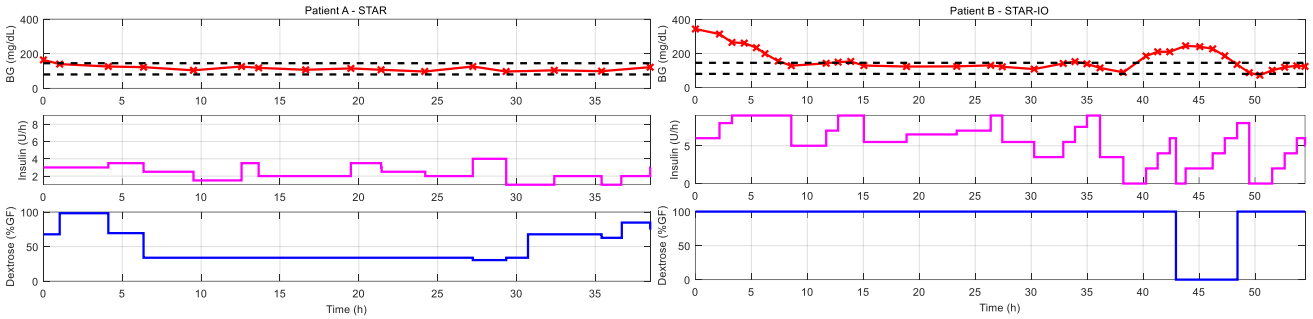

Figure 3. BG levels, insulin rate, and nutrition rate for Patient A (top) on STAR, and Patient B (bottom) on STAR-IO. Dashed line shows the 80-145 mg/dL target band.

reflecting the big tradeoff of measurement frequency to achieve high control quality, where too low a frequency can increase hypoglycemic risks and lower time in band, while too high a frequency leads to excessive clinical burden. The resulting median [IQR] BG is much higher than STAR, with 25% of BG measurements higher than 160 mg/dL. Finally, while being the standard of care in this ICU, more than 20% of interventions are changed by clinical staff, leading to important influence from clinical judgment on GC outcomes, hence questioning results and protocol design.

This analysis shows model-based computerized methods using key physiological parameters can result in safe and effective GC, while targeting lower intermediate glycemic ranges, which are associated with improved outcomes [3, 30, 31]. Hence, it also suggests future larger studies comparing GC results and clinical outcomes should ensure they can provide very similar control quality in both arms before assessing potential benefits or making any conclusions.

V. Conclusion

In this clinical trial, STAR achieved safe and effective GC, with an encouraging high %BG in target band, and similar nutritional intake than clinically set (STAR-IO). This high control quality was achieved with similar safety than the standard protocol targeting higher ranges. Thus, STAR provides safe and effective control to a lower 80-145 mg/dL target band, for all patients in this unit, as it has in others internationally. These promising results suggest the continuation of the trial.

REFERENCES

[1] K. C. McCowen, A. Malhotra, and B. R. Bistrian, "Stress-induced hyperglycemia," *Crit Care Clin*, vol. 17, pp. 107-24, Jan 2001.

[2] J. S. Krinsley, "Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients," *Mayo Clin Proc*, vol. 78, pp. 1471-8, Dec 2003.

[3] J. G. Chase, C. G. Pretty, L. Pfeifer, G. M. Shaw, J. C. Preiser, A. J. Le Compte, *et al.*, "Organ failure and tight glycemic control in the SPRINT study," *Crit Care*, vol. 14, p. R154, 2010.

[4] J. S. Krinsley, "Effect of an intensive glucose management protocol on the mortality of critically ill adult patients," *Mayo Clin Proc*, vol. 79, pp. 992-1000, Aug 2004.

[5] C. C. Reed, R. M. Stewart, M. Sherman, J. G. Myers, M. G. Corneille, N. Larson, *et al.*, "Intensive insulin protocol improves glucose control and is associated with a reduction in intensive care unit mortality," *J Am Coll Surg*, vol. 204, pp. 1048-54; discussion 1054-5, May 2007.

[6] G. Van den Berghe, P. Wouters, F. Weekers, C. Verwaest, F. Bruyninckx, M. Schetz, *et al.*, "Intensive insulin therapy in critically ill patients," *N Engl J Med*, vol. 345, pp. 1359-67, Nov 8 2001.

[7] J. C. Preiser, P. Devos, S. Ruiz-Santana, C. Melot, D. Annane, J. Groeneveld, *et al.*, "A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study," *Intensive Care Med*, vol. 35, pp. 1738-48, Oct 2009.

[8] F. M. Brunkhorst, C. Engel, F. Bloos, A. Meier-Hellmann, M. Ragaller, N. Weiler, *et al.*, "Intensive insulin therapy and pentastarch resuscitation in severe sepsis," *N Engl J Med*, vol. 358, pp. 125-39, Jan 10 2008.

[9] S. Finfer, D. R. Chittock, S. Y. Su, D. Blair, D. Foster, V. Dhingra, *et al.*, "Intensive versus conventional glucose control in critically ill patients," *N Engl J Med*, vol. 360, pp. 1283-97, Mar 26 2009.

[10] S. Finfer, B. Liu, D. R. Chittock, R. Norton, J. A. Myburgh, C. McArthur, *et al.*, "Hypoglycemia and risk of death in critically ill patients," *N Engl J Med*, vol. 367, pp. 1108-18, Sep 20 2012.

[11] M. Egi, R. Bellomo, E. Stachowski, C. J. French, and G. Hart, "Variability of blood glucose concentration and short-term mortality in critically ill patients," *Anesthesiology*, vol. 105, pp. 244-52, Aug 2006.

[12] J. C. Preiser and H. M. Straaten, "Glycemic control: please agree to disagree," *Intensive Care Med*, vol. 42, pp. 1482-4, Sep 2016.

[13] J. Gunst and G. Van den Berghe, "Blood glucose control in the ICU: don't throw out the baby with the bathwater!," *Intensive Care Med*, vol. 42, pp. 1478-81, Sep 2016.

[14] J. S. Krinsley, "Is It Time to Rethink Blood Glucose Targets in Critically Ill Patients?," *Chest*, vol. 154, pp. 1004-1005, Nov 2018.

[15] J. Dubois, T. Van Herpe, R. T. van Hooijdonk, R. Wouters, D. Coart, P. Wouters, *et al.*, "Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multicenter randomized controlled clinical trial," *Crit Care*, vol. 21, p. 212, Aug 14 2017.

[16] K. W. Stewart, C. G. Pretty, H. Tomlinson, F. L. Thomas, J. Homlok, S. N. Noemi, *et al.*, "Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis," *Ann Intensive Care*, vol. 6, p. 24, Dec 2016.

[17] J. G. Chase, T. Desaive, J. Bohe, M. Cnop, C. De Block, J. Gunst, *et al.*, "Improving glycemic control in critically ill patients: personalized care to mimic the endocrine pancreas," *Crit Care*, vol. 22, p. 182, Aug 2 2018.

[18] A. J. Le Compte, C. G. Pretty, J. Lin, G. M. Shaw, A. Lynn, and J. G. Chase, "Impact of variation in patient response on model-based control of glycaemia in critically ill patients," *Comput Methods Programs Biomed*, vol. 109, pp. 211-9, Feb 2013.

[19] J. G. Chase, J. C. Preiser, J. L. Dickson, A. Pironet, Y. S. Chiew, C. G. Pretty, *et al.*, "Next-generation, personalised, model-based critical care medicine: a state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them," *Biomed Eng Online*, vol. 17, p. 24, Feb 20 2018.

[20] V. Uyttendaele, J. L. Dickson, G. M. Shaw, T. Desaive, and J. G. Chase, "Untangling glycaemia and mortality in critical care," *Crit Care,* vol. 21, p. 152, Jun 24 2017.

[21] J. G. Chase, S. Andreassen, K. Jensen, and G. M. Shaw, "Impact of human factors on clinical protocol performance: a proposed assessment framework and case examples," *J Diabetes Sci Technol,* vol. 2, pp. 409-16, May 2008.

[22] F. Suhaimi, A. Le Compte, J. C. Preiser, G. M. Shaw, P. Massion, R. Radermecker, *et al.*, "What makes tight glycemic control tight? The impact of variability and nutrition in two clinical studies," *J Diabetes Sci Technol,* vol. 4, pp. 284-98, Mar 2010.

[23] V. Uyttendaele, J. L. Dickson, G. M. Shaw, T. Desaive, and J. G. Chase, "Virtual Trials of the NICE-SUGAR Protocol: The Impact on Performance of Protocol and Protocol Compliance," *IFAC-PapersOnline,* vol. 50, pp. 6672-6677, 2017.

[24] A. Evans, A. Le Compte, C. S. Tan, L. Ward, J. Steel, C. G. Pretty, *et al.*, "Stochastic targeted (STAR) glycemic control: design, safety, and performance," *J Diabetes Sci Technol,* vol. 6, pp. 102-15, Jan 2012.

[25] J. Lin, D. Lee, J. G. Chase, G. M. Shaw, A. Le Compte, T. Lotz, *et al.*, "Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care," *Comput Methods Programs Biomed,* vol. 89, pp. 141-52, Feb 2008.

[26] P. D. Docherty, J. G. Chase, and T. David, "Characterisation of the iterative integral parameter identification method," *Med Biol Eng Comput,* vol. 50, pp. 127-34, Feb 2012.

[27] K. W. Stewart, J. G. Chase, C. G. Pretty, and G. M. Shaw, "Nutrition delivery of a model-based ICU glycaemic control system," *Ann Intensive Care,* vol. 8, p. 4, Jan 10 2018.

[28] J. Lin, N. N. Razak, C. G. Pretty, A. Le Compte, P. Docherty, J. D. Parente, *et al.*, "A physiological Intensive Control Insulin-Nutrition-Glucose (ICING) model validated in critically ill patients," *Comput Methods Programs Biomed,* vol. 102, pp. 192-205, May 2011.

[29] J. L. Dickson, K. W. Stewart, C. G. Pretty, M. Flechet, T. Desaive, S. Penning, *et al.*, "Generalisability of a Virtual Trials Method for Glycaemic Control in Intensive Care," *IEEE Trans Biomed Eng,* vol. 65, pp. 1543-1553, Jul 2018.

[30] M. Signal, A. Le Compte, G. M. Shaw, and J. G. Chase, "Glycemic levels in critically ill patients: are normoglycemia and low variability associated with improved outcomes?," *J Diabetes Sci Technol,* vol. 6, pp. 1030-7, Sep 01 2012.

[31] S. Penning, J. G. Chase, J. C. Preiser, C. G. Pretty, M. Signal, C. Melot, *et al.*, "Does the achievement of an intermediate glycemic target reduce organ failure and mortality? A post hoc analysis of the Glucontrol trial," *J Crit Care,* vol. 29, pp. 374-9, Jun 2014.